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Original article

Synthesis and olfactoric activity of side-chain modified β-santalol analogues

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With our best wishes, dedicated to Professor Dr W. Fleischhacker on the occasion of his 70th birthday

Abstract – Three osmophoric points have been postulated to be necessary for the sandalwood scent of β-santalol derivatives. One of these points, close to the hydroxyl group, is highly specific on the stereochemistry and, in particular, on the molecular shape. The role of the 2-methyl group in the side chain of β-santalol derivatives was studied by replacement through a hydrogen atom, an ethyl or an isopropyl group. It turns out that any change at the 2-methyl substituent leads to the complete loss of sandalwood odour.
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structure–odour relationship / sandalwood odorant / β-santalol

1. Introduction

(−)-(*Z*)-β-Santalol (**1**), the main constituent of natural sandalwood oil, is an odour compound with typical sandalwood fragrance and is described as warm-woody, creamy and sweet with an animalic tonality [1–4]. The structure–odour properties of this compound and a series of derivatives were topics of interest in many investigations [5–18]. The structures of odour receptors and the corresponding mechanisms of interaction between the receptor protein and the odour molecules are more or less unknown. Therefore, the determination of essential structure elements can be only performed by molecular similarity studies within a series of sandalwood odour compounds and structurally similar, but non-odorous molecules. In a general study on sandalwood odour substances three osmophoric centres, which are important for this specific odour impression were found by 'Active Analog Approach' investigations [11]. These osmophoric parts of **1** are depicted in *figure 1*.

In this model, one of the important regions of the molecule is the functional group (A), mainly represented by a hydroxyl group. A second, very specific osmophoric point (B) occurs in the neighbourhood of this functional group. The third point (C) includes the bulky hydrophobic residue. The relative position of these osmophoric points, the distance between them and the stereospecifity are very important for the fragrance [11].

For the refinement of the model the osmophoric points were analysed in more detail taking into account both steric as well as electronic properties. The bulky substituent was already modified in several studies [6, 8, 9, 19–22], also investigations on the influence of the side-chain geometry on the sandalwood scent have been performed [12, 19, 23, 24]. Modifications of the functional group (A) [25–27] and of the substituent at the α-C-atom were studied, too [7].

The importance of the osmophoric centre B in this class of compounds was not proven up to now. The results obtained from 'Active Analog Approach' investigations showed that this substituent plays an important role for the odour of the compound, either

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exerting a steric (= shielding) effect on the neighbouring hydroxyl group, or as a sort of anchor group directing the essential hydroxyl moiety into the appropriate position for the necessary contact with the receptor. It may also act as a hydrophobic counterpart to the hydrophilic functional group. To answer this question, if the methyl group in this position is really essential for the sandalwood scent, derivatives with various substituents at the osmophoric point B have been synthesised: compound **2** with a smaller substituent—a hydrogen atom instead of the methyl group—and compounds **3** and **4** with larger substituents, an ethyl and an isopropyl group. The influence of the size of the substituents is discussed in the present work based on the olfaction of these newly synthesised β-santalol derivatives. Interestingly, within the class of campholenic aldehyde derivatives the replacement of the methyl neighbouring group by a bigger ethyl group has no influence on the odour impression [28].

In order to study the influence of the specific position of the osmophoric group B relative to the other centres, the (*E*)- and (*Z*)-configurated compounds are included.

2. Results: syntheses and olfactoric evaluation

2.1. Syntheses

As a starting substance for the preparation of the bicyclic alcohols **2**–**4**, we have chosen the commercially available bicyclic ketone **5**, which could be alkylated in a two-step process according to the procedure of Krotz et al. [29], first with bromomethyldioxolane and subsequently with methyl iodide leading to the ketone **6**. In accordance with the findings of Corey et al. [30], the more space demanding side chain assumes the *exo*-position, whereas the relatively small methyl group is forced into the cavity of the bicyclus, thus being *endo* at C-3. In case the order of sequence of the two alkylating steps is reversed, a mixture of both epimers is obtained. Cleavage of the acetals with diluted sulphuric acid—this more or less drastic condition furnishes better yields and a cleaner product—leads to the corresponding aldehyde **7**, as a suitable synthon for the following 'Wittig–Horner' reaction using 18-crown-6, potassium-bis-(trimethylsilyl)-amide and the appropriate alkyl phosphone esters[1] [32, 33]. Normally, this procedure provides threefold substituted olefinic esters with a high *Z*-selectivity (>80:20 [32]). However, we obtained **8** as a 33:67-, **9** as a 40:60- and **10** only as a 83:17-mixture of the corresponding *Z*/*E*-isomers. In comparison to **10**, which was used as the isomeric mixture for the next step, **8** and **9** could be separated into the pure *Z*- and *E*-compounds. In the ^{1}H-NMR spectrum of these compounds the signal of the olefinic proton at C-3′ shown as a multiplet in ***Z*-8**, triplet in ***Z*-9** and ***Z*-10**, could always be found characteristically upfield shifted compared to the same signal of the C-3′–H of ***E*-8**, ***E*-9** and ***E*-10**. In the case of both isomers of **8** and **9**, transformation of the ketone function at C-2 into the exocyclic methylene group was accomplished by 'Nozaki's' method with zinc dust and $TiCl_4$ as Lewis acid [34]. For the sterically more voluminous molecule **10** the TEBBE-reagent [35, 36] had to be used. Column chromatography followed by preparative TLC led to ***Z*-13** only in a very moderate yield. Finally, the last step, the reduction of the esters ***Z*-11**, ***E*-11**, ***Z*-12**, ***E*-12** and ***Z*-13** with DIBAH furnished the target products, namely the allylic alcohols ***Z*-** and ***E*-2**, ***Z*-** and ***E*-3** and ***Z*-4** (*figure 2*).

2.2. Olfactoric evaluation

An extensive odour evaluation was performed for all the newly synthesised compounds. The results are given in *table I*. As shown in the table, the scent of the compounds differs significantly and allows, therefore, to draw conclusions about the structure–activity relationships.

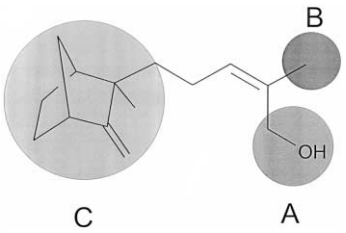

Figure 1. Osmophoric centres found for sandalwood odour compounds by 'Active Analog Approach' investigations shown for **1**.

[1] The side-chain synthons for **8** and **9** are commercially available, the appropriate one for **10** had to be prepared from 2-bromo-3-methyl-butyric acid via esterification, followed by an 'Arbuzov' reaction [31] with phosphoric acid triethyl ester.

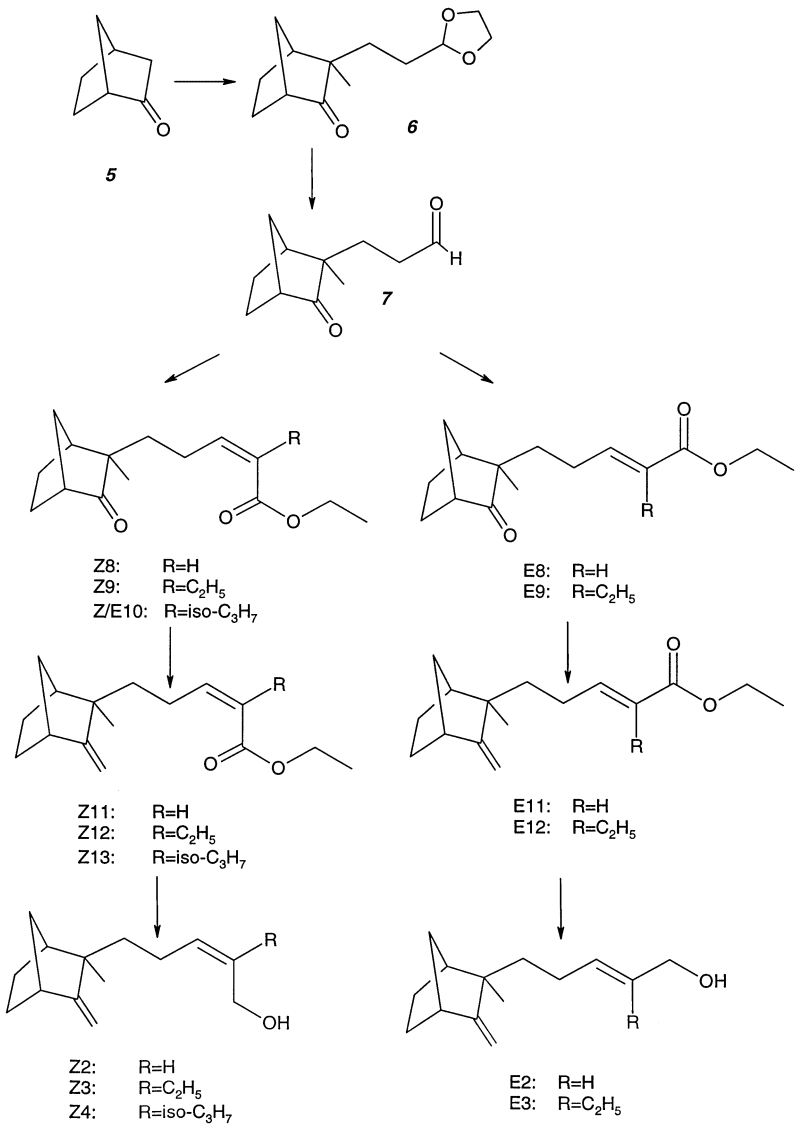

Figure 2. Syntheses of compounds ***Z*-2**–***Z*-4** and ***E*-2** and ***E*-3**.

As already postulated before [11], this hydrophobic region is indeed very sensitive to changes. The absence of the allylic methyl group deprives the β-santalol derivative from the sandalwood odour, the insertion of a more bulky substituent, such as ethyl or even isopropyl as well. The decrease of odour strength in ***E*-3** and ***Z*-4** is probably caused by an increase of molecular mass, thus reducing the volatility, a phenomenon, which is well known in fragrance chemistry. Based on these results it is ascertained that only the allylic methyl group possesses the suitable dimension allowing a close contact with the corresponding receptor.

3. Discussion

Following the model of sandalwood odour developed by the 'Active Analog Approach' study [11], a lot of structurally modified β-santalol derivatives have been synthesised in the past with the intention to get more information about the detailed structural requirements and the importance of the osmophoric parts for the association at the receptor site. Besides steric modifications, also the influence of the electronic parameters has been a centre of interest. A survey of the most important synthetic modifications is given in *figure 3.*

Table I. Odour description of side-chain modified β-santalol analogues.

Compound	Odour
***Z*-1**	pure sandalwood, warm, woody, creamy, sweet, animalic
***E*-1**	woody, medicinal
***Z*-2**	olibanum-like, leathery, reminiscent of castoreum, woody, very volatile
***E*-2**	spicy, olibanum-like, galbanum note, very volatile
***Z*-3**	spicy, herbaceous, later cedar wood note
***E*-3**	faint odour, like ***Z*-3**
***Z*-4**	very faint odour, soft woody, neither reminiscent to cedar wood nor to sandalwood

First of all, it has to be mentioned that the receptor odour molecule interaction is stereospecific. Investigations done by Krotz and Helmchen [29] show that only (−)-(*Z*)-β-santalol (**1**) possesses sandalwood fragrance. Such a stereoselectivity was also found for (+)-*tert*-butyl-bicyclo[4.4.0]decan-3-ol [37], (−)-(1′*S*)-Madrol® [38] and another more rigid campholenic aldehyde derivative, namely [1-methyl-2-(1,2,2-trimethylbicyclo[3.1.0]hex-3-yl-methyl)-cyclopropyl]-methanol [28], three synthetic compounds with clear sandalwood odour.

In *figure 3*, the modifications of β-santalol are drawn together with their contributions to sandalwood odour. Compounds with solid line arrows show no sandalwood scent anymore; this means that there might be a steric hindrance at the receptor, which disables the association of the odour molecule. Compounds with broken line arrows show sandalwood fragrance or at least a somewhat weaker sandalwood odour compared to β-santalol.

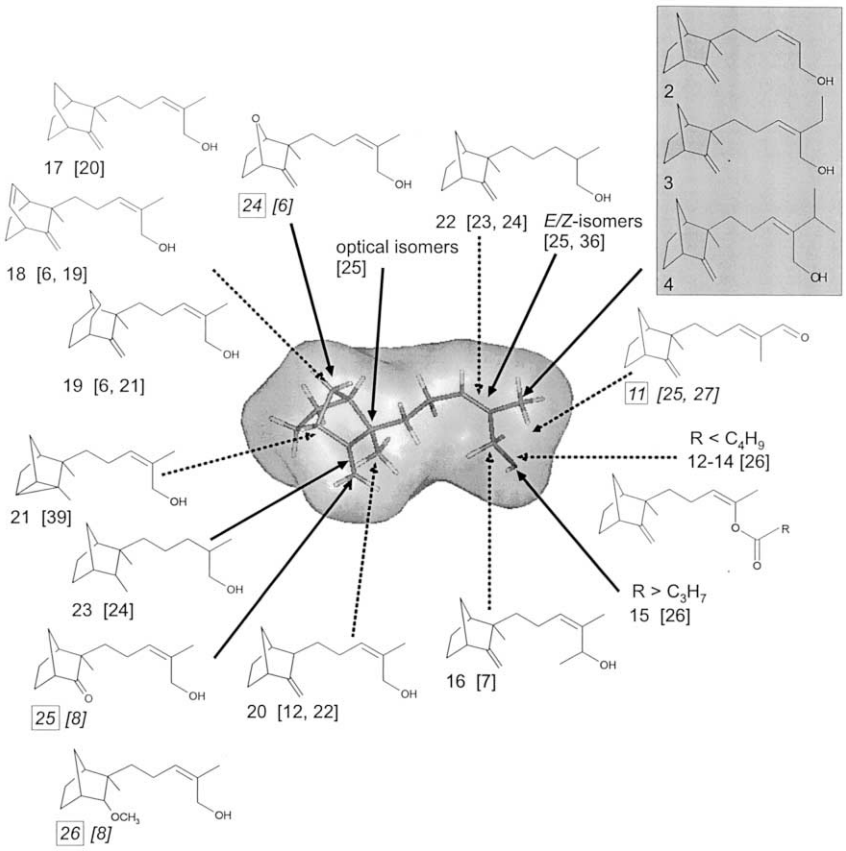

Figure 3. Structural and electrostatic modifications of β-santalol derivatives and their fragrance (sandalwood odour molecules are depicted with broken line arrows, non-sandalwood odour compounds with arrows drawn with solid lines). Derivatives with electrostatic modifications are indicated by squares.

Some modifications have been done at the functional group, the hydroxyl group, which, e.g. can be substituted by a carbonyl group (compound **11** [25, 27]). Esterification with formic acid (compound **12**), acetic acid (compound **13**) or propionic acid (compound **14**) forms sandalwood fragrant substances [26]. The use of higher carbonic acids, like butyric acid (yields compound **15**) or aromatic carbonic acids causes the loss of sandalwood scent. It is evident that this region is not very sensitive against structural changes as long as not too large groups are introduced. Methylation at the α-carbon atom (compound **16**) changes the odour to be aromatic, woody, with still some residual of the sandalwood note [7]. This again is an indication for a weaker steric influence of this part of the molecule, as long as the possibility to form a hydrogen bond remains. Also slight modifications in the bulky residue are without consequences for the odour quality. Substitution of the methylene bridge by an ethano bridge (yields compound **17**) [20], etheno bridge (compound **18**) [19], or by the larger propano bridge (compound **19**) [21], or even removal of the methyl group at the chiral carbon atom (compound **20**) [12, 22], does not influence the fragrance (see *figure 3*). (+)-(*Z*)-α-Santalol (**21**) [39], which shows differences in the ring-skeleton, possesses weak sandalwood odour. More complex is the situation in the case of side-chain modifications. Pure hydrogenation of the C=C double bond (compound **22**) does not affect the odour at all [23, 24], whereas the hydrogenation of both, the side-chain double bond and the exocyclic double bond (compound **23**), completely removes the sandalwood fragrance [24]. Generally, the *trans* (*E*)-double bond substituted compounds do not behave like sandalwood odorants, the *cis*-(*Z*)-configured derivatives show this odour [13, 29].

Changes of the electrostatic potential at the bulky residue (see *figure 3*) generally lead to compounds without sandalwood fragrance. Substitution of the methylene group by an oxygen atom in the norbornane skeleton (compound **24**) [6], or in the exocyclic C=C double bond (compound **25**) [8] as well as the substitution of this double bond by a methoxy group (compound **26**) destroys the scent [8].

4. Conclusions

As shown in the general overview (*figure 3*), both sterical as well as electronic properties are important for the association of the odour molecule at the specific receptor site. Generally, modifications of the electrostatic potential lead to the lack of sandalwood fragrance, the influence of the sterical changes depends on the region at the molecule. The osmophoric point A is not very sensitive to changes, similar as the bulky substituent C, but here some more sensitive molecule parts can be detected. Side-chain modifications are somewhat divergent, as some modifications have strong influence on the odour impression, some not. On the contrary, the stereospecific position of the osmophoric point B is very important for the fragrance. Referring to the newly synthesised compounds it could be shown that this osmophoric point is extremely sensitive to structural changes, because here only rather small modifications have a strong influence on the sandalwood scent. Replacement of the methyl group by a smaller substituent (a hydrogen atom) as well as by larger substituents (an ethyl or an isopropyl-residue) causes the complete loss of the sandalwood odour impression.

Evidently, only the methyl substituted compound fulfils all requirements for an association at a very sensitive and specific site of the receptor.

Van der Waals contacts of the methyl group may be necessary for the association of the compound at the receptor site, or the methyl group may force the hydroxyl moiety in a proper position to obtain a stronger interaction with the receptor protein.

5. Experimental protocols

GC analyses were carried out in a Shimadzu GC-14A, 30 m fused silica capillary column permabond SE-30-DF-0.25 (purity for the odour analysis: 99%). Mass spectra were recorded in a Hewlett–Packard MSD (GC: 5890; MS: 5970) spectrometer. IR spectra were acquired using a Perkin–Elmer-237 spectrometer as well as a Perkin–Elmer FT-IR spectrum 2000 spectrometer (bands are assigned in cm^{-1}). ^{1}H-NMR spectra were recorded in a Bruker AM 400 WB (400.13 MHz) using TMS as internal standard (at room temperature (r.t.) and in $CDCl_3$ if not otherwise indicated, δ values are given in ppm). ^{13}C-NMR spectra were recorded in the same spectrometer (Bruker AM 400 WB, 100.61 MHz) using the same conditions (*J*-modulated). For TL-chromatography, alumina sheets coated with silica gel 60 F_{254} (20×20 cm, layer thickness 0.2 mm, Merck no. 5554) were used. Prepar-

ative TLC was performed on PSC plates silica gel 60 $F_{254}S$ with concentration zone (20×20 cm, 2 mm layer thickness, Merck no. 13 793). Column chromatography for purification was performed with silica gel 60 filled glass columns (Merck no. 1.09385, particle size 0.040–0.063 mm).

*5.1. 3-[2-(1,3-Dioxolan-2-yl)-ethyl]-3-methyl-bicyclo[2.2.1]heptan-2-one (**6**)*

(1) A mixture of sodium amide (2.13 g, 54.54 mmol), hexamethyldisilazane (11.51 mL, 54.54 mmol) in 46 mL xylene was refluxed for 5 h and finally allowed to cool. Then, norbornan-2-one (**5**) (5 g, 45.45 mmol) was added and stirred for another 2 h at r.t. Upon addition of 2-(2-bromoethyl)-1,3-dioxolane (11.21 mL, 95.45 mmol) the mixture was refluxed for 1 h, allowed to cool and quenched with water followed by extraction with diethyl ether. The combined ethereal extracts were dried with magnesium sulphate. Evaporation of the solvent and subsequent distillation (kugelrohr) of the residue afforded 7.1 g of raw 3-[2-(1,3-dioxolan-2-yl)-ethyl]-bicyclo[2.2.1]heptan-2-one which were purified by column chromatography using ligroin–ethyl acetate = 80:20. Yield: 5.2 g (54.5%). $C_{12}H_{18}O_3$ (210.13).

(2) 3-[2-(l,3-Dioxolan-2-yl)-ethyl]-bicyclo[2.2.1]heptan-2-one (5.9 g, 28.09 mmol) was alkylated with methyl iodide (3.53 mL, 56.68 mmol) using the same procedure as above. Yield: 4.84 g (77%) of a colourless oil. Data: see Ref. [8].

*5.2. 3-(2-Methyl-3-oxo-bicyclo[2.2.1]heptan-2-yl)-propanal (**7**) ('2-keto-ekasantalal')*

An amount of 4.84 g (21.6 mmol) of **6** was dissolved in 10 mL of diethyl ether and stirred overnight with 72 mL 2 N H_2SO_4. Upon extraction of this mixture with diethyl ether, the combined organic phases were washed with water, dried with sodium sulphate and finally evaporated. With this residue the hydrolysis reaction was repeated. Yield: 3.04 g (78.2%) of **7** as a colourless, viscous oil. Data: see Ref. [8].

*5.3. (Z)/(E)-5-(3-Oxo-2-methyl-bicyclo[2.2.1]hept-2-yl)-2-pentenoic acid ethyl ester (**Z/E-8**)*

A solution of 2-phosphonoacetic acid triethyl ester (0.68 mL, 3.41 mmol) and freshly recrystallised 18-Crown-6 (4.43 g, 16.75 mmol) in 68 mL THF was cooled down to −80 °C and mixed with potassium-bis-(trimethylsilyl)-amide (0.5 M in toluene) (7 mL, 3.5 mmol). Afterwards, a solution of the aldehyde **7** (600 mg, 3.3 mmol) in THF was added dropwise and the mixture stirred for 4 h at −80 °C. Upon quenching with saturated NH_4Cl solution, extraction with diethyl ether followed. Afterwards, the combined ethereal extracts were dried with $MgSO_4$ and freed from the solvent by evaporation. The residue was distilled (kugelrohr) and yielded 1 g of the raw Wittig product (two isomers, 33% *Z*:67% *E*) which was purified by preparative TLC with ligroin–ethyl acetate (85:15) and some drops of MeOH (twofold development). Yield: zone 1 ***Z*-8** = 82 mg (30%), zone 2 ***E*-8** = 266 mg (48% relative to the amount used for this separation). $C_{15}H_{22}O_3$ (250.16). ***Z*-8**: IR (NaCl, liquid film): 1742, 1721, 1655, 1175; ^{1}H-NMR ($CDCl_3$): 1.0 (s, 3H, CH_3), 1.21 (t, 3H, CH_3), 1.25–1.9 (m, 8H), 2.28 (m, 1H), 2.50 (m, 1H, *H*–C-1), 2.60 (m, 2H), 4.10 (q, 2H, O*C*H_2), 5.69 (d, 1H, =CHCOOR), 6.10 (m, 1H, =C*H*R); ^{13}C-NMR ($CDCl_3$): 14.1 (CH_3), 19.0 (CH_3), 22.9 (CH_2), 23.7 (CH_2), 24.7 (CH_2), 33.3 (CH_2), 34.7 (CH_2/C-7), 43.7 (CH/C-4), 49.8 (C/C-3), 49.96 (CH/C-1), 59.7 (OCH_2), 119.8 (=CHCOOR), 149.4 (=CHR), 166.1 (C=O, ester), 221.8 (C=O, ketone). MS (*m*/*z*, relative intensity): 250, ([M^+], 23), 204 (100), 176 (46), 137 (22), 124 (32), 114 (35), 107 (76), 96 (60), 81 (53), 67 (84), 55 (44). ***E*-8**: ^{1}H-NMR ($CDCl_3$): 1.05 (s, 3H, CH_3), 1.28 (t, 3H, CH_3), 1.32–1.98 (m, 8H), 2.17 (m, 1H), 2.32 (m, 2H), 2.58 (m, 1H, *H*–C-1), 4.18 (q, 2H, O*C*H_2), 5.84 (d, 1H, =C*H*COOR), 6.96 (m, 1H, =CHR); ^{13}C-NMR ($CDCl_3$): 14.1 (CH_3), 18.9 (CR_3), 22.9 (CH_2), 24.5 (CH_2), 26.8 (CH_2), 32.4 (CH_2), 34.6 (CH_2/C-7), 43.8 (CH/C-4), 49.4 (C/C-3), 49.8 (CH/C-1), 59.9 (OCH_2), 121.2 (=CHCOOR), 148.2 (=CHR), 166.2 (C=O, ester), 221.1 (C=O, ketone).

*5.4. (E)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-pentenoic acid ethyl ester (**E-11**)*

To a suspension of zinc dust (929.6 mg, 14.22 mmol) and dibromomethane (0.33 mL, 4.74 mmol) in THF (8 mL) was added a 1 M solution of $TiCl_4$ in CH_2Cl_2 (74 mL, 1.74 mmol) at 25 °C dropwise. A rapid, exothermic discolouring to dark brown could be observed. After 15 min a solution of ketoester ***E*-8** (395 mg, 1.58 mmol) in THF was added dropwise and stirred for another 60 h at r.t.. Upon dilution with diethyl ether and subsequent quenching with 1 M HCl the mixture was extracted with diethyl ether. The combined ethereal extracts were washed with brine, dried with $MgSO_4$ and evaporated. The residue was purified by preparative TLC with

ligroin–ethyl acetate (95:5) and some drops of MeOH. Yield: 96 mg (24.5%). $C_{16}H_{24}O_2$ (248.17). IR (NaCl, liquid film): 3070, 1735, 1655, 1180, 970, 880; ^{1}H-NMR ($CDCl_3$): 1.01 (s, 3H, CH_3), 1.29 (t, 3H, CH_3), 1.25–1.8 (m, 8H), 2.01 (m, 1H, C-4), 2.1 (m, 1H), 2.25 (m, 1H), 2.69 (m, 1H, C-1), 4.18 (q, 2H, OCH_2), 4.48 (s, 1H, exocyl. =CH_2), 4.74 (s, 1H, exocycl. =CH_2), 5.84 (d, 1H, =C*H*COOR), 6.97 (m, 1H, =C*H*R); ^{13}C-NMR ($CDCl_3$): 14.3 (CH_3), 23.7 (CH_2), 25.2 (CH_3), 28.2 (CH_2), 28.97 (CH_2), 37.03 (CH_2/C-7), 37.14 (CH_2), 44.6 (C/C-3), 45.1 (CH/C-4), 46.7 (CH/C-1), 60.1 (OCH_2), 99.7 (exocycl. =CH_2), 120.9 (=CHCOOR), 149.5 (=CHR), 166.1 (=CR_2/C-2), 166.7 (C=O). MS (*m*/*z*, relative intensity): 248 ([M^+], 17), 220 (11), 180 (39), 160 (28), 135 (48), 119 (32), 107 (47), 93 (99), 91(100), 79 (87), 77 (55).

*5.5. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-pentenoic acid ethyl ester (**Z-11**)*

The same procedure as above, but this time using 680.1 mg (10.4 mmol) zinc dust, 0.24 mL (3.5 mmol) dibromomethane in 6 mL THF and 1.3 mL (1.27 mmol) $TiCl_4$ solution in methylene chloride yielded after preparative TLC 58 mg (20.2%) of **Z-11**. $C_{16}H_{24}O_2$ (248.17). ^{1}H-NMR ($CDCl_3$): 1.05 (s, 3H, CH_3), 1.29 (t, 3H, CH_3), 1.2–1.75 (m, 8H), 2.05 (m, 1H, C-4), 2.59 (m, 1H), 2.68 (m, 2H, *H*–C-1), 4.18 (q, 2H, OCH_2), 4.48 (s, 1H, exocycl. =CH_2), 4.73 (s, 1H, exocycl. =CH_2), 5.72 (d, 1H, =C*H*COOR), 6.22 (m, 1H, =CHR); ^{13}C-NMR ($CDCl_3$): 14.3 (CH_3), 23.6 (CH_2), 25.21 (CH_2), 25.25 (CH_3), 29.1 (CH_2), 37.1 (CH_2/C-7), 38.1 (CH_2), 44.9 (C/C-3), 45.1 (CH/C-4), 46.7 (CH/C-1), 59.8 (OCH_2), 99.4 (exocycl. =CH_2), 119.3 (=CHCOOR), 150.5 (=CHR), 166.7 (C=O); MS (*m*/*z*, relative intensity): 248 ([M^+], 17), 220 (11), 180 (39), 160 (28), 135 (48), 119 (32), 107(47), 93 (99), 91(100), 79 (87), 77 (55).

*5.6. (E)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-pent-2-enol (**E-2**)*

A solution of 385 mg (1.55 mmol) of ester ***E*-11** in dry methylene chloride was cooled down to −78 °C and mixed with a 20% solution of diisobutylaluminiumhydride (DIBAH) (6.86 mL, 9.65 mmol) in *n*-hexane. Stirring overnight caused a warming up of the reaction mixture to r.t. and afforded another cooling, but this time only to −20 °C. Then 2 mL of a methanol–water (1:1) mixture was added and stirring proceeded for another 3 h, this time at r.t., as long as the precipitation of a thick, white sediment could be noticed, which was filtered through Celite®. The residue was washed with ethyl acetate and the filtrate freed from the solvent by evaporation. Purification of this residue was performed by preparative TLC with ligroin–ethyl acetate (70:30) and some drops of MeOH (twofold development). Yield: 94 mg (29.4%). $C_{14}H_{22}O$ (206.15). IR (NaCl, liquid film): 3360, 3080,1665, 1375, 970, 880; ^{1}H-NMR ($CDCl_3$): 1.0 (s, 3H, CH_3), 1.2–1.8 (m, 8H), 1.99 (m, 2H, *H*–C-4), 2.1 (m, 1H), 2.67 (m, 1H, C-1), 4.08 (d, 2H, CH_2OH), 4.47 (s, 1H, exocycl. =CH_2), 4.72 (s, 1H, exocycl. =CH_2), 5.68 (2m, 2H, RC*H*=CHR); ^{13}C-NMR ($CDCl_3$): 23.6 (CH_2), 25.2 (CH_3), 28.05 (CH_2), 28.99 (CH_2), 37.0 (CH_2/C-7), 38.4 (CH_2), 44.7 (C/C-3), 45.1 (CH/C-4), 46.7 (CH/C-1), 63.7 (CH_2OH), 99.3 (exocycl. =CH_2), 128.5 (RCH=), 133.6 (=CHR), 166.5 (=CR_2/C-2); MS (*m*/*z*, relative intensity): 188 ([M^+−18], 5), 173 (5), 159 (6), 145 (8), 133 (9), 121(21), 105 (27), 94 (100), 93 (67), 79 (58), 67 (27).

*5.7. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-pent-2-enol (**Z-2**) ('2′-desmethyl-β-santalol')*

The same procedure as above using 290 mg (1.17 mmol) ester ***Z*-11** and 5.2 mL (7.27 mmol) DIBAH in *n*-hexane yielded after preparative TLC 81 mg (33.6%) of ***Z*-2**. $C_{14}H_{22}O$ (206.15). Anal. Calc. C, 81.56; H, 10.76. Found: C, 81.78; H, 10.89%. ^{1}H-NMR ($CDCl_3$): 1.02 (s, 3H, CH_3), 1.2–1.75 (m, 8H), 1.98 (m, 2H, *H*–C-4), 2.13 (m, 1H), 2.68 (m, 1H, C-1), 4.21 (d, 2H, CH_2OH), 4.47 (s, 1H, exocycl. =CH_2), 4.72 (s, 1H, exocycl. =CH_2), 5.58 (2m, 2H, RC*H*=C*H*R); ^{13}C-NMR ($CDCl_3$): 23.5 (CH_2), 23.7 (CH_2), 25.2 (CH_3), 29.0 (CH_2), 37.0 (CH_2/C-7), 38.9 (CH_2), 44.8 (C/C-3), 45.1 (CH/C-4), 46.6 (CH/C-1), 58.5 (CH_2OH), 99.4 (exocycl. =CH_2), 128.03 (RCH=), 133.3 (=CHR), 166.4 (=CR_2/C-2); MS (*m*/*z*, relative intensity): 188 ([M^+−18], 5), 173 (5), 159 (6), 145 (8), 133 (9), 121(21), 105 (27), 94 (100), 93 (67), 79 (58), 67 (27).

*5.8. (Z)/(E)-5-(3-Oxo-2-methyl-bicyclo[2.2.1]hept-2-yl)-2-ethyl-2-pentenoic acid ethyl ester (**Z-9**, **E-9**)*

A solution of 2-phosphonobutyric acid triethyl ester (0.67 mL, 2.84 mmol) and freshly recrystallised 18-Crown-6 (3.7 g, 13.96 mmol) in 57 mL THF was cooled down to −80 °C and mixed with potassium-bis-(trimethylsilyl)-amide (0.5 M in toluene) (5.8 mL, 2.92 mmol). Afterwards, a solution of the aldehyde **7** (500 mg, 2.78 mmol) in THF was added dropwise and the reaction continued as already described above. The raw

Wittig product was purified by preparative TLC with pentane–ethyl acetate (90:10) and some drops of MeOH.

Yield: zone 1 (***Z*-9**) = 82 mg (26.5%), zone 2 (***E*-9**) = 186 mg (40.2% relative to the amount used for this separation). $C_{17}H_{26}O_3$ (278.18). ***Z*-9**: ^{1}H-NMR ($CDCl_3$): 1.02 (t, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.31 (t, 3H, CH_3), 1.3–2 (m, 8H), 2.26 (q, 2H, allyl. C*H*$_2$), 2.32–2.5 (m, 3H), 2.58 (m, 1H, C-1), 4.22 (q, 2H, OC*H*$_2$), 5.80 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 13.5 (CH_3), 14.3 (CH_3), 19.1 (CH_3), 23.1 (CH_2), 24.3 (CH_2), 24.7 (CH_2), 27.4 (CH_2), 33.9 (CH_2), 34.8 (CH_2/C-7), 43.8 (CH/C-4), 49.9 (C/C-3), 50.04 (CH/C-1), 59.99 (OCH_2), 133.9 (=CR_2), 139.5 (=CHR), 168.03 (C=O, ester), 222.1 (C=O, ketone); MS (*m*/*z*, relative intensity): 278 ([M$^+$], 2), 232 (58), 205 (8), 163 (11), 137 (14), 124 (12), 109 (100), 96 (49), 81(36), 67 (42), 55 (22). ***E*-9**: ^{1}H-NMR ($CDCl_3$): 1.02 (t, 3H, CH_3), 1.07 (s, 3H, CH_3), 1.29 (t, 3H, CH_3), 1.3–2.4 (m, 11H), 2.32 (m, 2H, allyl. C*H*$_2$), 2.59 (m, 1H, C-1), 4.19 (q, 2H, OC*H*$_2$), 6.68 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 13.95 (CH_3), 14.2 (CH_3), 19.1 (CH_3), 19.97 (CH_2), 23.07 (CH_2), 23.13 (C*H*$_2$), 24.6 (CH_2), 33.4 (CH_2), 34.7 (CH_2/C-7), 43.9 (CH/C-4), 49.7 (C/C-3), 50.0 (CH/C-1), 59.96 (OCH_2), 134.2 (=CR_2), 140.8 (=CHR), 167.6 (C=O, ester), 221.6 (C=O, ketone).

*5.9. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-ethyl-2-pentenoic acid ethyl ester (**Z-12**)*

Zinc dust (535.4 mg, 8.19 mmol), dibromomethane (0.19 mL, 2.73 mmol) in 4.5 mL THF, a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1 mL, 1.001 mmol) and keto ester ***Z*-9** (253 mg, 0.91 mmol) in THF were used and processed as described above. Purification was performed by preparative TLC with pentane–ethyl acetate (98:2) and some drops of MeOH (twofold development). Yield: 63 mg (25.2%). $C_{18}H_{28}O_2$ (276.2). IR (NaCl, liquid film): 3070, 1720,1660, 1040, 880; ^{1}H-NMR ($CDCl_3$): 1.03 (t, 3H, CH_3), 1.03 (s, 3H, CH_3), 1.31 (t, 3H, CH_3), 1.25–1.75 (m, 8H), 2.02 (m, 1H, C-4), 2.27 (m, 3H, allyl. C*H*$_2$ also q), 2.5 (m, 1H), 2.67 (m, 1H, C-1), 4.22 (q, 2H, OC*H*$_2$), 4.48 (s, 1H, exocycl. C*H*$_2$), 4.72 (s, 1H, exocycl. C*H*$_2$), 5.83 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 13.6 (CH_3), 14.3 (CH_3), 23.7 (CH_2), 25.3 (CH_3), 25.6 (CH_2), 27.6 (CH_2), 29.1 (CH_2), 37.1 (CH_2), 38.6 (CH_2), 44.9 (C/C-3), 45.2 (CH/C-4), 46.7 (CH/C-1), 60.0 (OCH_2), 99.3 (exocycl. =CH_2), 133.3 (=CR_2), 140.2 (=CHR), 166.7 (=CR_2, C-2), 168.4 (C=O); MS (*m*/*z*, relative intensity): 277 ([M$^+$+1], 4), 276 (23), 247 (5), 230 (21), 202 (14), 162 (25), 135 (38), 107 (35), 94 (100), 79 (57), 67 (36).

*5.10. (E)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-ethyl-2-pentenoic acid ethyl ester (**E-12**)*

Zinc dust (863.5 mg, 13.21 mmol), dibromomethane (0.31 mL, 4.40 mmol) in 7.3 mL THF, a 1 M solution of $TiCl_4$ in CH_2Cl_2 (1.6 mL, 1.61 mmol) and keto ester ***E*-9** (408 mg, 1.47 mmol) in THF were used and processed as described above. Purification was performed by preparative TLC with pentane–ethyl acetate (98:2) and some drops of MeOH (twofold development). Yield: 135 mg (33.4%). $C_{18}H_{28}O_2$ (276.2). IR (NaCl, liquid film): 3070, 1720,1650, 1040, 880; ^{1}H-NMR ($CDCl_3$): 1.04 (t, 3H, CH_3), 1.05 (s, 3H, CH_3), 1.29 (t, 3H, CH_3), 1.22–1.75 (m, 8H), 2.03 (m, 1H, C-4), 2.05–2.25 (m, 2H), 2.33 (q, 2H, allyl. C*H*$_2$), 2.69 (m, 1H, C-1), 4.19 (q, 2H, OC*H*$_2$), 4.48 (s, 1H, exocycl. C*H*$_2$), 4.73 (s, 1H, exocycl. C*H*$_2$), 6.72 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 14.1 (CH_3), 14.3 (CH_3), 20.04 (CH_2), 23.7 (CH_2), 24.5 (CH_2), 25.2 (CH_3), 29.02 (CH_2), 37.1 (CH_2), 38.02 (CH_2), 44.8 (C/C-3), 45.1 (CH/C-4), 46.7 (CH/C-1), 60.3 (OCH_2), 99.6 (exocycl. =C*H*$_2$), 133.7 (=CR_2), 142.0 (=CHR), 166.2 (=CR_2, C-2), 167.9 (C=O); MS (*m*/*z*, relative intensity): 277 ([M$^+$+1], 3), 276 (18), 247 (4), 230 (14), 202 (9), 162 (23), 135 (37), 107 (31), 94 (100), 79 (55), 67 (39).

*5.11. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-ethyl-pent-2-enol (**Z-3**) ('2'-ethyl-β-santalol')*

As already described above ester ***Z*-12** (244 mg, 0.88 mmol) and a 20% solution of DIBAH in *n*-hexane (3.91 mL, 5.5 mmol) were processed. Preparative TLC with pentane–ethyl acetate (85:15) and some drops of MeOH furnished finally 42 mg (20.3%) of the target product. $C_{16}H_{26}O$ (234.18). Anal. Calc. C, 82.06; H, 11.19. Found: C, 82.26; H, 11.27%. IR (NaCl, liquid film): 3326, 3070, 1656, 1017, 878; ^{1}H-NMR ($CDCl_3$): 1.02 (s, 3H, CH_3), 1.04 (t, 3H, CH_3), 1.2–1.7 (m, 8H), 1.9–2.2 (m, 2H), 2.02 (m, 1H, C-4), 2.14 (q, 2H, allyl. C*H*$_2$), 2.67 (m, 1H, C-1), 4.17 (s, 2H, C*H*$_2$OH), 4.47 (s, 1H, exocycl. C*H*$_2$), 4.72 (s, 1H, exocycl. C*H*$_2$), 5.32 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 12.8 (CH_3), 23.5 (CH_2), 23.7 (CH_2), 25.2 (CH_3), 27.8 (CH_2), 29.1 (CH_2), 37.1 (CH_2), 38.5 (CH_2), 44.9 (C/C-3), 45.2 (CH/C-4), 46.7 (CH/C-1), 60.4 (CH_2OH), 99.3 (exocycl. =CH_2), 127.8 (=CHR), 139.6 (=CR_2), 166.6 (=CR_2, C-2); MS (*m*/*z*, relative intensity): 216 ([M$^+$−18], 5), 203 (1), 187 (7), 161(4), 148 (7), 133 (5), 122 (24), 107 (13), 94 (100), 79 (35), 67 (18).

*5.12. (E)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-ethyl-pent-2-enol (**E-3**)*

Ester ***E*-12** (407 mg, 1.47 mmol), 6.52 mL (9.17 mmol) of a 20% solution of DIBAH in *n*-hexane in dry CH_2Cl_2 were processed as described above. Finally, the same purification procedure furnished 105 mg (30.4%) of the allylic alcohol ***E*-3**. $C_{16}H_{26}O$ (234.18). IR (NaCl, liquid film): 3330, 3070, 1656, 1014, 877; ^{1}H-NMR ($CDCl_3$): 1.03 (s, 3H, CH_3), 1.03 (t, 3H, CH_3), 1.2–1.7 (m, 8H), 1.9–2.2 (m, 2H), 2.02 (m, 1H, C-4), 2.13 (q, 2H, allyl. C*H*$_2$), 2.67 (m, 1H, C-1), 4.04 (s, 2H, C*H*$_2$OH), 4.47 (s, 1H, exocycl. C*H*$_2$), 4.72 (s, 1H, exocycl. C*H*$_2$), 5.38 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 13.4 (CH_3), 21.01 (CH_2), 23.2 (CH_2), 23.7 (CH_2), 25.2 (CH_3), 29.04 (CH_2), 37.02 (CH_2), 39.1 (CH_2), 44.8 (C/C-3), 45.1 (CH/C-4), 46.7 (CH/C-1), 66.8 (CH_2OH), 99.3 (exocycl. =CH_2), 126.6 (=CHR), 140.2 (=CR_2), 166.6 (=CR_2, C-2); MS (*m*/*z*, relative intensity): 216 ([M^+−18], 8), 203 (3), 187 (11), 161 (6), 148 (10), 133 (8), 122 (25), 107 (16), 94 (100), 79 (38), 67 (19).

5.13. 2-Phosphono-(3-methyl-butyric acid)-triethyl ester

2-Bromo-3-methyl-butyric acid ethyl ester (2.5 g, 11.96 mmol, freshly prepared by azeotropic esterification of 2-bromo-isovaleric acid and ethanol) under argon atmosphere was refluxed with phosphoric acid triethyl ester (2.05 mL, 11.96 mmol) overnight (oil bath, 200 °C). Purification of the mixture was performed by distillation (kugelrohr, 70 °C, 0.2 Torr) and then by preparative TLC with diethyl ether–ethyl acetate (70:30). $C_{11}H_{23}O_5P$ (266.10). IR (NaCl, liquid film): 1735,1392, 1369, 1257, 1029; ^{1}H-NMR ($CDCl_3$): 1.10 (d, 3H, CH_3), 1.15 (d, 3H, CH_3), 1.27–1.35 (m, 9H, 3OCH_2C*H*$_3$), 2.38 (m, 1H, *i*-Pr–C*H*), 2.72 (m, 1H, P–C*H*), 4.12–4.25 (m, 6H, 3OC*H*$_2$); ^{13}C-NMR ($CDCl_3$): 14.07 (CH_3), 16.2 (CH_3), 16.3 (CH_3), 21.4 (CH_3), 21.6 (CH_3), 28.2 (*i*-Pr–CH), 52.4 and 52.2 (P–CH), 61.01 (OCH_2), 62.2 (OCH_2), 62.3 (OCH_2), 169.2 (C=O); MS (*m*/*z*, relative intensity): 267 ([M^++1], 2), 251 (9), 224 (100), 197 (77), 179 (48), 169 (28), 152 (71), 137 (27), 123 (80), 105 (30), 81 (43).

*5.14. (Z)/(E)-5-(3-Oxo-2-methyl-bicyclo[2.2.1]hept-2-yl)-2-isopropyl-2-pentenoic acid ethyl ester (**Z/E-10**)*

A solution of 2-phosphono-3-(methylbutyric acid)-triethyl ester (755.3 mg, 2.84 mmol) and freshly recrystallised 18-Crown-6 (3.7 g, 13.96 mmol) in 57 mL THF was cooled down to −80 °C and mixed with potassium-bis-(trimethylsilyl)-amide (0.5 M in toluene) (5.8 mL, 2.92 mmol). Afterwards, a solution of the aldehyde **7** (500 mg, 2.78 mmol) in THF was added dropwise and the reaction continued as already described above. The raw Wittig product was purified by preparative TLC with pentane–ethyl acetate (90:10) and some drops of MeOH. Yield: 93 mg (11.5%) (mixture of ***Z*-10** and ***E*-10**). GC: isomeric ratio = 83:17 (*Z*/*E*), reaction time = 14.1 and 14.5 min. $C_{18}H_{28}O_3$ (292.22). IR (NaCl, liquid film): 2966, 1743, 1713, 1638, 1178, 1055; ^{1}H-NMR ($CDCl_3$): 0.96–0.99 (m, 9H, 3CH_3), 1.1–1.9 (m, 9H), 1.24 (t, 3H, CH_3), 2.24 (m, 2H, allyl. C*H*$_2$), 2.51 (m, 1H, C-1), 2.60 (m, 1H, allyl. C*H*), 4.16 (q, 2H, OC*H*$_2$), 5.59 (t, 1H, =C*H*), [6.48 (t, =C*H*) of ***E*-10**]; ^{13}C-NMR ($CDCl_3$): 14.3 (CH_3), 19.1 (CH_3), 21.7 (2CH_3), 23.1 (CH_2), 24.3 (CH_2), 24.6 (CH_2), 31.3 (allyl. CH), 33.96 (CH_2), 34.8 (CH_2), 43.9 (CH/C-4), 49.91 (C/C-3), 49.99 (CH/C-1), 60.02 (OCH_2), 134.3 (=CH/***Z*-10**), 138.1 (=CR_2/***E*-10**), 139.2 (=CR_2/***Z*-10**), 139.7 (=CH/***E*-10**), 167.6 (C=O, ester, ***E*-10**), 168.8 (C=O, ester, ***Z*-10**), 222.01 (C=O, ketone); MS (*m*/*z*, relative intensity): 292 ([M^+], 4), 277 (3), 246 (74), 231 (7), 219 (19), 203 (13), 177 (4), 151 (7), 137 (14), 123 (60), 95 (100).

*5.15. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-isopropyl-2-pentenoic acid ethyl ester (**Z-13**)*

A solution of the ketoester mixture ***Z*/*E*-10** (210 mg, 0.72 mmol) in dry THF (6.3 mL) was cooled down to 0 °C. Then TEBBE reagent (0.5 M in toluene, 1.75 mL) was added dropwise and stirred for 30 min at 0 °C. Stirring was carried out for 24 h at r.t. Afterwards, the mixture was quenched by the addition of 10–20 mL diethyl ether and as many drops of dry methanol required till no reaction could be observed anymore. Then the suspension was filtered through Celite®. Finally, the filtrate was washed with diethyl ether and freed from the solvent. The deep orange–red coloured, very viscous residue was roughly purified by column chromatography over Al_2O_3. The final purification of this mixture (GC: isomeric ratio = 85:15 *Z*/*E*, reaction time = 13.9 and 14.3 min) was performed by preparative TLC with ligroin–diethyl ether (97:3) and some drops of MeOH (fourfold development). Yield: 44 mg (21.1%) pure ***Z*-13**. $C_{19}H_{30}O_2$ (290.24). IR (NaCl, liquid film): 3063, 1716, 1656, 1052, 878; ^{1}H-NMR($CDCl_3$): 0.94–0.99 (m, 9H, 3 CH_3), 1.11–1.62 (m, 8H), 1.25 (t, 3H, CH_3), 1.93 (m, 1H, C-4), 2.09–2.4 (m, 2H), 2.61 (m, 2H, allyl. C*H*, *H*–C-1), 4.16 (q, 2H, OC*H*$_2$), 4.41 (s, 1H, exocycl.

=CH_2), 4.65 (s, 1H, exocycl. =CH_2), 5.60 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 14.3 (CH_3), 21.75 (CH_3), 21.80 (CH_3), 23.7 (CH_2), 25.3 (CH_3), 25.6 (CH_2), 29.1 (CH_2), 31.4 (allyl. CH), 37.1 (CH_2), 38.7 (CH_2), 44.9 (C/C-3), 45.2 (CH/C-4), 46.7 (CH/C-1), 60.04 (OCH_2), 99.4 (exocycl. =CH_2), 135.04 (=CH), 138.7 (=CR_2), 166.6 (=CR_2, C-2), 169.1 (C=O); MS (*m*/*z*, relative intensity): 290 ([M^+], 1), 275 (1), 244 (2), 229 (3), 201 (2), 176 (8), 135 (18), 122 (21), 107 (19), 94 (100), 79 (44).

*5.16. (Z)-5-(2-Methyl-3-methylene-bicyclo[2.2.1]hept-2-yl)-2-isopropyl-pent-2-enol (**Z-4**) ('2′-isopropyl-β-santalol')*

As already described above ester ***Z*-13** (174 mg, 0.6 mmol) in dry CH_2Cl_2 and a 20% solution of DIBAH in *n*-hexane (2.65 mL, 3.73 mmol) were processed. Preparative TLC with pentane–diethyl ether (65:35) and some drops of MeOH furnished 140 mg of a still impure target compound which could be completely purified by another TLC, but this time on alumina sheets coated with silica gel 60 F_{254} (20×20 cm, layer thickness 0.2 mm, Merck no. 5554) with ligroin–diethyl ether (70:30) (and some drops of MeOH, threefold development).

Yield: 26 mg (17.5) pure ***Z*-4**. $C_{17}H_{28}O$ (248.21). Anal. Calc. C, 82.26; H, 11.37. Found: C, 82.49; H, 11.48%. IR (NaCl, liquid film): 3350, 3063, 1656, 1018, 878; ^{1}H-NMR ($CDCl_3$): 0.96–0.99 (m, 9H, 3CH_3), 1.11–1.62 (m, 8H), 1.89–2.16 (m, 2H), 1.95 (m, 1H, C-4), 2.35 (m, 1H, allyl. CH), 2.60 (m, 1H, C-1), 4.1 (s, 2H, CH_2OH), 4.41 (s, 1H, exocycl. =CH_2), 4.65 (s, 1H, exocycl. =CH_2), 5.28 (t, 1H, =C*H*); ^{13}C-NMR ($CDCl_3$): 22.0 (2 CH_3), 23.6 (CH_2), 23.8 (CH_2), 25.3 (CH_3), 29.1 (CH_2), 32.9 (allyl. CH), 37.1 (CH_2), 39.5 (CH_2), 44.9 (C/C-3), 45.2 (CH/C-4), 46.7 (CH/C-1), 59.6 (CH_2OH), 99.3 (exocycl. =CH_2), 127.4 (=CH), 144.1 (=CR_2), 166.7 (=CR_2, C-2); MS (*m*/*z*, relative intensity): 230 ([M^+−18], 1), 215 (1), 187 (4), 167 (3), 147 (2), 135 (3), 122 (22), 105 (11), 94 (100), 79 (41), 67 (25).

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References

[1] Brunke E.J., Klein E., in: Mookherjee B.D., Mussinan C.J. (Eds.), Essential Oils, Allured Publishing, Wheaton, IL, 1981, pp. 83–103.

[2] Brunke E.J., Klein E., in: Theimer E. (Ed.), Fragrance Chemistry. The Science of the Sense of Smell, Academic Press, New York, 1982, pp. 397–431.

[3] Ohloff G., Winter B., Fehr C., in: Müller P.M., Lamparsky D. (Eds.), Perfumes. Art, Science and Technology, Elsevier Applied Science, London, 1991, pp. 287–330.

[4] Weyerstahl P., J. Prakt. Chem. 336 (1994) 95–109.

[5] Buchbauer G., Leonhartsberger K., Winiwarter S., Wolschann P., Helv. Chim. Acta 75 (1992) 174–183.

[6] Buchbauer G., Lebada Ph., Spreitzer H., Wolschann P., Liebigs Ann. (1995) 1693–1696.

[7] Buchbauer G., Spreitzer H., Zechmeister-Machhart F., Weiss-Greiler P., Wolschann P., Arch. Pharm. 330 (1997) 112–114.

[8] Buchbauer G., Spreitzer H., Zechmeister-Machhart F., Klinsky A., Weiss-Greiler P., Wolschann P., Eur. J. Med. Chem. 33 (1998) 463–470.

[9] Brunke E.J., Dragoco-Report 28 (1981) 251–262.

[10] Frater G., Bajgrowicz J.A., Kraft P., Tetrahedron 54 (1998) 7633–7703.

[11] Buchbauer G., Hillisch A., Mraz K., Wolschann P., Helv. Chim. Acta 77 (1994) 2286–2296.

[12] Rossiter K.J., Chem. Rev. 96 (1996) 3201–3240.

[13] Brunke E.J., Dragoco-Report 30 (1983) 27–32.

[14] Buchbauer G., Klinsky A., Weiss-Greiler P., Wolschann P., J. Mol. Model. 6 (2000) 425–432.

[15] Chastrette M., SAR QSAR Environ. Res. 3–4 (1997) 215–254.

[16] Rognon C., Chastrette M., Eur. J. Med. Chem. 29 (1994) 595–609.

[17] Chastrette M., Zakarya D., Pierre C., Eur. J. Med. Chem. 25 (1990) 433–440.

[18] Zakarya D., Cherqaoui D., Esseffar M., Villemin D., Cense J.M., J. Phys. Org. Chem. 10 (1997) 612–622.

[19] Buchbauer G., Spreitzer H., Öckher B., Pretterklieber C., Piringer I., Wolschann P., Monatsh. Chem. 126 (1995) 467–472.

[20] Spreitzer H., Rösslhuber I., Kienzl H., Dörrer E., Buchbauer G., Monatsh. Chem. 121 (1990) 195–201.

[21] Buchbauer G., Spreitzer H., Zechmeister-Marchart F., Haunschmidt C., Tröscher F., Monatsh. Chem. 127 (1996) 747–753.

[22] Kretschmar, H.C., Erman, W.F., US Patent, 3,673,261, 1972.

[23] Fanta W.I., Erman W.F., Tetrahedron Lett. 47 (1969) 4155–4156.

[24] Fanta W.I., Erman W.F., J. Org. Chem. 37 (1972) 1624–1630.

[25] Mookherjee, B.D., Trenkle, R.W., Wilson R.A., in: Woidich, H., Buchbauer, G. (Eds.), Proc. 12th Int. Cong. Flav. Fragr. Essent. Oils, 4–8 October 1992, Vienna, Austria, Aust. Assoc. Flav. and Frag. Industry, 1992, pp. 234–262.

[26] Arctander St., Perfumes and Flavor Chemistry, Mont Clair, NJ, 1969.

[27] Demole E., Demole C., Enggist P., Helv. Chim. Acta 59 (1976) 737–746.

[28] Bajgrowicz J.A., Frater G., Enantiomer 5 (2000) 225–234.

[29] Krotz A., Helmchen G., Tetrahedron: Asymmetry 1 (1990) 537–540.

[30] Corey E.J., Hartmann R., Vatakencherry P.A., J. Am. Chem. Soc. 84 (1962) 2611–2614.

[31] Arbuzov B.A., Pure Appl. Chem. 9 (1964) 307–335.

[32] Still W.C., Gennari C., Tetrahedron Lett. 24 (1983) 4405–4408.

[33] Gokel G.W., Cram D.J., Liotta C.L., Harris H.P., Cook F.L., J. Org. Chem. 39 (1974) 2445–2446.

[34] Takai K., Hotta Y., Oshima K., Nozaki H., Bull. Chem. Soc. Jpn. 53 (1980) 1698–1702.

[35] Pine S.H., Pettit R.J., Geib G.D., Cruz S.G., Gallego C.H., Tijerina T., Pine R.D., J. Org. Chem. 50 (1985) 1212–1216.

[36] Tebbe F.N., Parshall G.W., Reddy G.S., J. Am. Chem. Soc. 100 (1978) 3611–3613.

[37] Buchbauer G., Spreitzer H., Swatonek H., Wolschann P., Tetrahedron: Asymmetry 3 (1992) 197–198.

[38] Buchbauer G., Lebada P., Wiesinger L., Weiss-Greiler P., Wolschann P., Chirality 9 (1997) 380–385.

[39] Sell C., Perfumer and Flavorist 25 (2000) 67–73.